ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	SANOFI-AVENTIS GMBH OSTERREICH SATURN Tower Leonard-Bernstein-Straße 10 A-1220 Vienna Austria	Tritace 1,25 mg-Tabletten Tritace 2,5 mg-Tabletten Tritace 5 mg-Tabletten Tritace 10 mg-Tabletten	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	HYPREN	1,25mg 2,5mg 5mg	Capsule	Oral
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	HYPREN	10mg	Tablet	Oral
Belgium	SANOFI-AVENTIS BELGIUM Culliganlaan 1C B-1831 Diegem Belgium	Tritace 1,25 mg, comprimés Tritace 2,5 mg, comprimés Tritace 5 mg, comprimés Tritace 10 mg, comprimés	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Belgium	Aventis Pharma S.A. Boulevard de la Plaine, 9 B-1050 Bruxelles	Tazko 5 mg, comprimés à liberation prolongée	5 mg	prolonged-release tablet	oral
Belgium	Aventis Pharma S.A. Boulevard de la Plaine, 9 B-1050 Bruxelles	Tazko 2,5 mg, comprimés à liberation prolongée	2,5 mg	prolonged-release tablet	oral
Belgium	SANOFI-AVENTIS BELGIUM Culliganlaan 1C B-1831 Diegem Belgium	Tritace 10	10 mg	Capsule	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Belgium	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussels Belgium	Ramace 1,25 mg Ramace 2,5 mg Ramace 5 mg	1,25 mg 2,5 mg 5 mg	Tablet	Oral
Bulgaria	SANOFI-AVENTIS BULGARIA EOOD Alexandar Stamboliyski blvd. 103 office building Sofia Tower, fl. 8, Sofia 1303 Bulgaria	Tritace 2.5 Tritace 5 Tritace 10	2.5 mg 5 mg 10 mg	Tablet	Oral
Cyprus	SANOFI-AVENTIS CYPRUS LTD 14 Charalambou Mouskou street 2015 – Nicosia Cyprus	Triatec	2.5 mg 5 mg 10 mg	Tablet	Oral
Czech Republic	sanofi-aventis, s.r.o. Evropská 2590/33c 16000 Praha 6 Czech Republic	Tritace 1.25 Tritace 2.5 Tritace 5 Tritace 10	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Czech Republic	AVENTIS PHARMA DEUTSCHLAND GMBH Industriepark Höchst 65926 Frankfurt am Main Germany	RAMIPRIL WINTHROP	1.25 mg 2.5 mg 5 mg	Capsule	Oral
Denmark	SANOFI-AVENTIS DENMARK A/S Slotsmarken 13 DK-2970 Hoersholm Denmark	Triatec	1.25 mg 2.5 mg 5 mg	Tablet	Oral
Denmark	SANOFI-AVENTIS DENMARK A/S Slotsmarken 13 DK-2970 Hoersholm	Triatec	10 mg	Capsule, hard	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Denmark				
Estonia	SANOFI-AVENTIS ESTONIA OÜ Pärnu mnt. 139 E/2 11317 Tallinn Estonia	Cardace	5 mg 10 mg	Tablet	Oral
Estonia	SANOFI-AVENTIS DEUTSCHLAND GMBH Industriepark Hoechst D-65926 Frankfurt am Main Germany	Cardace	2.5 mg	Tablet	Oral
Finland	SANOFI-AVENTIS OY Huopalahdentie 24 00350 Helsinki Finland	Cardace	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Finland	SANOFI-AVENTIS OY Huopalahdentie 24 00350 Helsinki Finland	Cardace	10 mg	Capsule	Oral
Finland	SANOFI-AVENTIS OY Huopalahdentie 24 00350 Helsinki Finland	Ramipril medgenerics 1.25 mg tabletti Ramipril medgenerics 2.5 mg tabletti Ramipril medgenerics 5 mg tabletti Ramipril medgenerics 10 mg tabletti	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
France	SANOFI AVENTIS FRANCE 1-13, boulevard Romain Rolland 75014 Paris France	Triatec 1.25 mg comprime Triatec 2.5 mg comprime sécable Triatec 5 mg comprime sécable Triatec 10 mg comprime sécable Triateckit, comprime sécable Ramikit, comprime sécable	1.25 mg 2.5 mg 5 mg 10 mg 2.5 mg / 5 mg / 10 mg 2.5 mg /5 mg/ 10mg	Tablet	Oral
France	SANOFI AVENTIS FRANCE 1-13, boulevard Romain Rolland	Triatec faible 1,25 mg, gélule Triatec 2.5 mg, gélule	1.25 mg 2.5 mg	Capsule	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	75014 Paris France	Triatec 5 mg, gélule	5 mg		
France	SANOFI AVENTIS FRANCE 1-13, boulevard Romain Rolland F-75014 Paris France	RAMIPRIL WINTHROP 1.25 MG RAMIPRIL WINTHROP 2.5 MG, COMPRIME SECABLE RAMIPRIL WINTHROP 5 MG, COMPRIME SECABLE RAMIPRIL WINTHROP 10 MG, COMPRIME SECABLE	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Germany	SANOFI-AVENTIS DEUTSCHLAND GMBH Industriepark Hoechst D-65926 Frankfurt am Main Germany	Delix 2,5 mg Tabletten Delix 5 mg Tabletten Delix protect 10 mg Tabletten Delix HOPE 10 mg Tabletten Delix HOPE startset Delix protect startset	2.5 mg 5 mg 10 mg 10 mg 2.5 mg/ 5mg /10mg 2.5 mg/ 5mg /10mg	Tablet	Oral
Germany	SANOFI-AVENTIS DEUTSCHLAND GMBH Industriepark Hoechst D-65926 Frankfurt am Main Germany	Ramipril protect 2,5 mg Tabletten Ramipril protect 5 mg Tabletten Ramipril protect 10 mg Tabletten Ramipril protect startset	2.5 mg 5 mg 10 mg 2.5 mg/ 5mg /10mg	Tablet	Oral
Germany	WINTHROP ARZNEIMITTEL GmbH Urmitzer Str. 5 56218 Mülheim-Kärlich Germany	Ramilich 2.5 mg Tabletten Ramilich 5 mg Tabletten Ramilich 10 mg Tabletten Ramilich startset	2.5 mg 5 mg 10 mg 2.5 mg/ 5mg /10mg	Tablet	Oral
Germany	WINTHROP ARZNEIMITTEL GmbH Urmitzer Str. 5 56218 Mülheim-Kärlich Germany	RamiWin 2,5 mg Tabletten RamiWin 5 mg Tabletten RamiWin 10 mg Tabletten	2.5 mg 5 mg 10 mg	Tablet	Oral
Germany	AVENTIS PHARMA	Delix 1,25 mg Tabletten	1.25 mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	DEUTSCHLAND GmbH 65926 Frankfurt am Main Germany				
Germany	AVENTIS PHARMA DEUTSCHLAND GmbH 65926 Frankfurt am Main Germany	Delix 1,25 mg Kapseln Delix P 2,5 mg Kapseln Delix P 5 mg Kapseln Delix P 10 mg Kapseln	1.25 mg 2.5 mg 5 mg 10 mg	Capsule, hard	Oral
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Vesdil 1,25 mg Kapseln Vesdil 2,5 mg kapseln Vesdil 5 mg Kapseln	1,25 mg 2,5 mg 5 mg	Capsule, hard	Oral
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Vesdil 1,25 mg Tabletten Vesdil 2,5 mg Tabletten Vesdil N 2,5 mg Tabletten Vedil 5 mg Tabletten Vesdil N 5 mg Tabletten Vesdil protect 10 mg Tabletten	1,25 mg 2,5 mg 2,5 mg 5 mg 5 mg 10 mg	Tablets	Oral
Greece	SANOFI-AVENTIS AEBE 348, Syngrou Av. - Building A 176 74 Kallithea Greece	Triatec	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Hungary	SANOFI-AVENTIS PRIVATE CO LTD H-1045 Budapest Tó u. 1.-5. Hungary	Tritace mite 1.25 mg tablet Tritace 2.5 mg tablet Tritace 5 mg tablet Tritace 10 mg tablet	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Hungary	SANOFI-AVENTIS PRIVATE CO LTD H-1045 Budapest Tó u. 1.-5. Hungary	Ramipril prevent 1.25 mg tablet Ramipril prevent 2.5 mg tablet Ramipril prevent 5 mg tablet Ramipril prevent 10 mg tablet	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Hungary	Zentiva HU Kft	Ramipril - Zentiva 1.25mg	1.25 mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Népfürdo u.22 1138 Budapest Hungary	Ramipril - Zentiva 2.5mg Ramipril - Zentiva 5mg Ramipril - Zentiva 10mg	2.5 mg 5 mg 10 mg		
Iceland	-				
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus, Dublin 24, Ireland	Tritace 1.25mg tablets Tritace 2.5mg tablets Tritace 5mg tablets Tritace 10mg tablets	1.25mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus Dublin 24 Ireland	Tritace 1.25mg capsules Tritace 2.5mg capsules Tritace 5mg capsules Tritace 10mg capsules	1.25 mg 2.5 mg 5. mg 10 mg	Capsule	Oral
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus Dublin 24 Ireland	Loavel 1.25mg Loavel 2.5mg Loavel 5mg Loavel 10mg	1.25mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus Dublin 24 Ireland	Loavel 1.25mg capsules Loavel 2.5mg capsules Loavel 5mg capsules Loavel 10mg capsules	1.25 mg 2.5 mg 5. mg 10 mg	Capsule	Oral
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus Dublin 24 Ireland	Ramipril 1.25mg tablets Ramipril 2.5mg tablets Ramipril 5mg tablets Ramipril 10mg tablets	1.25mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus Dublin 24 Ireland	Ramipril 1.25mg capsules Ramipril 2.5mg capsules Ramipril 5mg capsules Ramipril 10mg capsules	1.25 mg 2.5 mg 5. mg 10 mg	Capsule	Oral
Italy	SANOFI-AVENTIS SPA Viale Bodio, 37/b 20158 Milano	Triatec 1,25 Triatec Triatec 5	1.25 mg 2.5 mg 5 mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Italy	Triatec Ramipril sanofi-aventis	10 mg 1.25 mg 2.5 mg 5 mg 10 mg		
Italy	AstraZeneca S.p.A Palazzo Volta Via Francesco Sforza 20080 Basiglio (MI) Italy	Unipril 1,25 mg compresse Unipril 2,5 mg compresse Unipril 5 mg compresse Unipril 10 mg compresse	1.25mg 2.5mg 5mg 10mg	Tablet	Oral
Italy	Polifarma S.p.A. Viale Dell' Arte, 69 I – 00144 Roma Italy	Quark Quark Quark Quark	1.25mg 2.5mg 5mg 10mg	Tablet	Oral
Latvia	sanofi-aventis Latvia SIA Kr.Valdemara 33-8 LV1010 - Riga Latvia	Cardace	2.5 mg 5 mg 10 mg	Tablet	Oral
Lithuania	UAB SANOFI-AVENTIS LIETUVA A. Juozapavičiaus g. 6/2 LT-09310 Vilnius Lithuania	Cardace	2.5 mg 5 mg 10 mg	Tablet	Oral
Luxembourg	SANOFI-AVENTIS BELGIUM Culliganlaan 1C B-1831 Diegem Belgium	Tritace 1,25 mg, comprimés Tritace 2,5 mg, comprimés Tritace 5 mg, comprimés Tritace 10 mg, comprimés	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Luxembourg	SANOFI-AVENTIS BELGIUM Culliganlaan 1C B-1831 Diegem	Tritace	10 mg	Capsule	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Belgium				
Luxembourg	NV AstraZeneca SA Egide Van Ophemstraat 110 B-1180 Brussels Belgium	Ramace 1,25 mg Ramace 2,5 mg Ramace 5 mg	1,25 mg 2,5 mg 5 mg	Tablet	Oral
Malta	-				
Netherlands	SANOFI-AVENTIS NETHERLANDS B.V. Kampenringweg 45 D-E (toren D en E) NL-2803 PE Gouda The Netherlands P.O. Box 2043 NL-2800 BD Gouda The Netherlands	Tritace 1.25 Tritace 2.5 Tritace 5 Tritace 10	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Netherlands	SANOFI-AVENTIS NETHERLANDS B.V. Kampenringweg 45 D-E (toren D en E) NL-2803 PE Gouda The Netherlands	Tritace 1.25 Tritace 2.5 Tritace 5 Tritace 10	1.25 mg 2.5 mg 5 mg 10 mg	Capsule	Oral
Norway	SANOFI-AVENTIS NORGE AS Strandveien 15 P.O.Box 133 NO-1325 Lysaker Norway	Triatec	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Norway	SANOFI-AVENTIS NORGE AS Strandveien 15 P.O.Box 133 NO-1325 Lysaker	Triatec	10 mg	Capsule	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Norway				
Norway	WINTHROP MEDICAMENTS 1-13 Boulevard Romain Rolland F-75159 Paris, Cedex 14 France	Ramipril winthrop	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Poland	SANOFI-AVENTIS DEUTSCHLAND GMBH D-65926 Frankfurt am Main Germany	Tritace 2.5 Tritace 5 Tritace 10	2.5 mg 5 mg 10 mg	Tablet	Oral
Portugal	Sanofi-Aventis Produtos Farmacêuticos, s.a. Empreendimento Lagoas Park, Edificio 7 - 3º Piso 2740-244 Porto Salvo Portugal	Triatec	2.5 mg 5 mg 10 mg	Tablet	Oral
Portugal	Sanofi-Aventis Produtos Farmacêuticos, s.a. Empreendimento Lagoas Park, Edificio 7 - 3º Piso 2740-244 Porto Salvo Portugal	Triatec	1.25 mg 2.5 mg 5 mg 10 mg	Capsule	Oral
Romania	AVENTIS PHARMA DEUTSCHLAND GMBH Brüningstraße 50 65926 Frankfurt am Main Germany	Tritace	2.5 mg 5 mg 10 mg	Tablet	Oral
Romania	SC ZENTIVA S.A. Bulevardul Theodor Pallady, nr. 50, sector 3 Bucuresti ROMANIA	Zenra 2.5 Zenra 5 Zenra 10	2.5 mg 5 mg 10 mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Slovak Republic	SANOFI-AVENTIS SLOVAKIA s.r.o. Žilinská 7-9 81105 Bratislava Slovak Republic	Tritace	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Slovenia	SANOFI-AVENTIS D.O.O. Dunajska cesta 119 1000 Ljubljana Slovenia	Tritace 1,25 mg teblete Tritace 2,5 mg tablete Tritace 5 mg tablete Tritace 10 mg tablete Tritace Startset	1.25 mg 2.5 mg 5 mg 10 mg 2,5 mg/ 5 mg/ 10 mg	Tablet	Oral
Spain	SANOFI-AVENTIS S.A. Josep Pla 2 08019 Barcelona Spain	Acovil	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Sweden	sanofi-aventis AB Box 14142 167 14 Bromma Sweden	Triatec Triatec H.O.P Triatec Start	1.25 mg 2.5 mg 5 mg 10 mg 2,5 mg/5 mg/10 mg 2,5 mg/5 mg/10 mg	Tablet	Oral
Sweden	WINTHROP MEDICAMENTS 1-13, Boulevard Romain Roland F-75014 Paris France	Ramipril winthrop	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
Sweden	AstraZeneca Sverige SE-151 85 Södertälje Sweden	Pramace	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
			Start pack (1,25 + 2,5 +5 mg)		
Sweden	AstraZeneca Sverige SE-151 85 Södertälje Sweden	Pramace	10 mg	Capsule	Oral
United Kingdom	AVENTIS PHARMA LTD 50 Kings Hill Avenue Kings Hill West Malling Kent ME19 4AH Trading as: Sanofi-aventis One Onslow Street Guildford Surrey GU1 4YS UK	Tritace 1.25 mg tablets Tritace 2.5 mg tablets Tritace 5 mg Tablets Tritace 10 mg tablets	1.25 mg 2.5 mg 5 mg 10 mg	Tablet	Oral
United Kingdom	HOECHST MARION ROUSSEL LTD. Denham Uxbridge UB9 5HP Trading as: Aventis Pharma 50 Kings Hill Avenue Kings Hill West Malling Kent ME19 4AH Or Sanofi-aventis One Onslow Street Guildford Surrey GU1 4YS	Tritace 1.25 mg Tritace 2.5 mg Tritace 5 mg Tritace 10 mg	1.25 mg 2.5 mg 5 mg 10 mg	Capsule	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	UK				
United Kingdom	AVENTIS PHARMA LTD 50 Kings Hill Avenue Kings Hill West Malling Kent ME19 4AH Trading as: Sanofi-aventis One Onslow Street Guildford Surrey GU1 4YS UK	Tritace Titration Pack	2.5mg /5mg/10mg	Tablet	Oral
United Kingdom	AVENTIS PHARMA LTD 50 Kings Hill Avenue Kings Hill West Malling Kent ME19 4AH Trading as: Sanofi-aventis One Onslow Street Guildford Surrey GU1 4YS UK	Tritace titration pack	2.5 mg 5.0 mg 10 mg	Capsule	Oral
United Kingdom	AVENTIS PHARMA LTD 50 Kings Hill Avenue Kings Hill West Malling Kent ME19 4AH Trading as: Sanofi-aventis One Onslow Street	Tritace Tablet Titration Pack	2.5mg 5.0mg 10mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Guildford Surrey GU1 4YS UK				

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF TRITACE AND ASSOCIATED NAMES (SEE ANNEX I)

Tritace contains ramipril, a second-generation nonsulfhydryl angiotensin converting enzyme inhibitor (ACE-I). Tritace was included in the list of products for Summary of Products Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended, as the above-mentioned medicinal product does not have the same SPC across EU Member States, Iceland and Norway.

Critical Evaluation
A number of areas of disharmony in the product information for Tritace have been evaluated by the CHMP and a revised product information was adopted. The main areas for harmonisation were: the sections 4.1, 4.2, 4.3, 4.4 and 4.6 of the summary of product information (SPC).

4.1 Therapeutic Indication

The current indication of ramipril in hypertension differs among the EU countries. The CHMP adopted the harmonised indication: *"Treatment of hypertension".*

Regarding the therapeutic indications for heart failure, the MAH proposed the wording***: "****Treatment of congestive heart failure".* The CHMP, considering the previous harmonisations referrals for enalapril, perindopril and lisinopril, adopted the harmonised indication*: "Treatment of symptomatic heart failure".*

The indication for cardiovascular prevention is justified by the results of HOPE study. There are differences, however, in the results obtained from various trials (HOPE, EUROPA, PEACE, and PART 2).
The Rapporteurs are of the opinion that amended wording, the lower age limit of 55 years, is recommended. Selective inclusion of one secondary endpoint- all cause mortality- is not recommended.
The CHMP adopted the following:
"Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with: i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or ii) diabetes with at least one cardiovascular risk factor".

The nephroprotection indication presented the major area of disagreement. In conclusion, the CHMP agreed the following indication: "*Treatment of renal disease*
-Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria

-Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor

-Manifest glomerular non-diabetic nephropathy as defined by macroproteinuria ≥ 3g/da"

The MAH proposed indication "*Secondary prevention after MI in patients with heart failure"* has been justified on the basis of the: Acute Infarction Ramipril Efficacy Study (AIRE).
Considering the available data the CHMP adopted the following indication:
"Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started >48 hours following acute myocardial infarction".

4.2 Posology and Method of Administration

Hypertension

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control.
Tritace and associated names may be used in monotherapy or in combination with other classes of antihypertensive medicinal products.

CV prevention
The MAH proposed the following wording based on international guidelines: "*Instead of increasing the dose above 5 mg* Tritace *and associated names daily, the addition of another drug, e.g. of a diuretic or a calcium-antagonist may be considered".* The CHMP agreed that the correctness of this last sentence is questionable and that no substance specific data were presented and therefore deleted this comment.
The time frame for dose escalation of 2 to 4 weeks appears appropriate based on individual variability.
The CHMP agreed the following:
"The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control. Tritace *and associated names may be used in monotherapy or in combination with other classes of antihypertensive medicinal products".*

Treatment of renal disease
The CHMP agreed that in patients with diabetes and microalbuminuria the recommended initial dose is 1.25 mg of Tritace once daily. In patients with diabetes and at least one cardiovascular risk the initial dose shold be 2.5 mg once a day. And finally, for patients with non diabetic nephropathy macroproteinuria ≥3gm/day, the recommended initial dose is 1.25 mg of Tritace once daily.

Symptomatic Heart failure
In all countries where the congestive heart failure indication has been approved the initial recommended dose is 0.25 mg daily and the maximum permitted dose is 10 mg daily. In most countries the dose is doubled every 1-2 weeks, except in Hungary where the duration is 2-3 weeks.
The proposals are acceptable with some improvements. In conclusion, the CHMP endorsed the following:
"In patients stabilised on diuretic therapy, the recommended initial dose is 1.25 mg daily Tritace *and associated names should be titrated by doubling the dose every one to two weeks up to a maximum daily dose of 10 mg. Two administrations per day are preferable".*

Secondary prevention after acute myocardial infarction
In all countries where the post myocardial infarction indication has been approved the initial recommended dose is 2.5 mg twice daily. However in 6 countries the starting dose is 1.25 mg to 2.5 mg twice daily. The maximal dose is 10 mg daily. The dose titration steps and target dose are based on the result of the AIRE study. The MAH calls on a high level of evidence for ACE-Is administered in the first 24 hours following acute myocardial infarction (MI) in international recommendations, to justify initiating therapy with 24 hours of MI at the lowest dose of 1.25 mg daily (that used as first dose in the heart failure indication), provided that stable haemodynamic conditions are met and the regulatory precedent with lisinopril wording.

The CHMP, considered that in the absence of substance specific supportive data in this post myocardial infarction (MI) 24 hour interval, agreed the following:
"After 48 hours, following myocardial infarction in a clinically and haemodynamically stable patient, the starting dose is 2.5 mg twice daily for three days. If the initial 2.5 dose in not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day the treatment should be withdraw"
(See SPC for Titration and maintenance dose)

4.3 Contraindications
There are contraindications present in one or several local SPCs. In summary, pregnancy and lactation should be amended in line with PhVWP recommendations on ACE-I
The following should be added to the contraindication:

Ramipril must not be used in patients in patients with hypotensive or haemodynamically unstable states
The CHMP adopted the following contraindication:
- "Hypersensitivity to ramipril, to any of the excipients or any other ACE inhibitors (see section 6.1)
- History of hereditary or idiopathic angioedema
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
-2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)"

4.4 Special Warnings and Precautions for Use
The CHMP adopted the following wording in order to implement this section:
-" *Renal Impairment: the warning should be expanded to include not just treatment in patients with renal impairment but the risk of subsequent renal impairment, risk factors and need for early discontinuation.*
-Agranulatocytosis: the warning should be expanded to include bone marrow depression and other effects on blood.
-Hypotension and renal dysfunction after acute myocardial infarction occurred more frequently with ramipril than placebo in the target population in the AIRE study.
- Transient or persistent heart failure post MI
- Monitoring of renal function
-Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough".

4.6 Pregnancy and Lactation
The CHMP recommended a contraindication only for the second and third trimester of pregnancy in line with PhVWP wording on use of AEC-I in pregnancy. However the company challenged this view and proposed a contraindication through out pregnancy, based on data from the ramipril pregnancy register.
The text agreed in the PhVWP of this warning doesn't encourage or propose the use of ACE inhibitors during the first trimester of the pregnancy on the contrary once the pregnancy is detected the prescriber has to stop the use of ACE inhibitors and to change if it is necessary for another anti-hypertensive agent as soon as possible. This change of the text is to ensure it doesn't suggest an immediate artificial abortion, which is not justified by the clinical experiences collected till now.
In conclusions, the CHMP adopted a harmonised wording in line with PhVWP wording on use of AEC-I in pregnancy. In conclusion, the CHMP adopted a harmonised wording according to the PhVWP recommendations.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Tritace and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

NAME OF THE MEDICINAL PRODUCT

TRITACE and associated names (see Annex I) 1.25 mg tablets
TRITACE and associated names (see Annex I) 2.5 mg tablets
TRITACE and associated names (see Annex I) 5 mg tablets
TRITACE and associated names (see Annex I) 10 mg tablets

TRITACE and associated names (see Annex I) 1.25 mg hard capsules
TRITACE and associated names (see Annex I) 2.5 mg hard capsules
TRITACE and associated names (see Annex I) 5 mg hard capsules
TRITACE and associated names (see Annex I) 10 mg hard capsules

[See Annex I - To be completed nationally]

QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Tablet
Hard capsule

[To be completed nation ally]

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

- Treatment of hypertension.

- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
    - manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
    - diabetes with at least one cardiovascular risk factor (see section 5.1).

- Treatment of renal disease:
    - Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
    - Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section 5.1),
    - Manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day (see section 5.1).

- Treatment of symptomatic heart failure.

- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

POSOLOGY AND METHOD OF ADMINISTRATION

Oral use.

It is recommended that TRITACE is taken each day at the same time of the day.
TRITACE can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2).
TRITACE has to be swallowed with liquid. It must not be chewed or crushed.

Adults

Diuretic-Treated patients
Hypotension may occur following initiation of therapy with TRITACE; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with TRITACE (see section 4.4).
In hypertensive patients in whom the diuretic is not discontinued, therapy with TRITACE should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of TRITACE should be adjusted according to blood pressure target.

Hypertension

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control.
TRITACE may be used in monotherapy or in combination with other classes of antihypertensive medicinal products.

Starting dose
TRITACE should be started gradually with an initial recommended dose of 2.5 mg daily.
Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision (see section 4.4).

Titration and maintenance dose
The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose of TRITACE is 10 mg daily. Usually the dose is administered once daily.

Cardiovascular prevention

Starting dose
The recommended initial dose is 2.5 mg of TRITACE once daily.

Titration and maintenance dose
Depending on the patient's tolerability to the active substance, the dose should be gradually increased. It is recommended to double the dose after one or two weeks of treatment and - after another two to three weeks - to increase it up to the target maintenance dose of 10 mg TRITACE once daily.

See also posology on diuretic treated patients above.

Treatment of renal disease

In patients with diabetes and microalbuminuria:

Starting dose:
The recommended initial dose is 1.25 mg of TRITACE once daily.

Titration and maintenance dose
Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

In patients with diabetes and at least one cardiovascular risk

Starting dose:
The recommended initial dose is 2.5 mg of TRITACE once daily.

Titration and maintenance dose
Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the daily dose to 5 mg TRITACE after one or two weeks and then to 10 mg TRITACE after a further two or three weeks is recommended. The target daily dose is 10 mg.

In patients with non- diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day.

Starting dose:
The recommended initial dose is 1.25 mg of TRITACE once daily.

Titration and maintenance dose
Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

Symptomatic heart failure

Starting dose
In patients stabilized on diuretic therapy, the recommended initial dose is 1.25 mg daily.

Titration and maintenance dose
TRITACE should be titrated by doubling the dose every one to two weeks up to a maximum daily dose of 10 mg. Two administrations per day are preferable.

Secondary prevention after acute myocardial infarction and with heart failure

Starting dose
After 48 hours, following myocardial infarction in a clinically and haemodynamically stable patient, the starting dose is 2.5 mg twice daily for three days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day the treatment should be withdrawn.

See also posology on diuretic treated patients above.

Titration and maintenance dose
The daily dose is subsequently increased by doubling the dose at intervals of one to three days up to the target maintenance dose of 5 mg twice daily.
The maintenance dose is divided in 2 administrations per day where possible.
If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to treat these patients, it is recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increase.

Special populations

Patients with renal impairment
Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):
- if creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;
- if creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;
- if creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg;
- in haemodialysed hypertensive patients: ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment (see section 5.2)
In patients with hepatic impairment, treatment with TRITACE must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg TRITACE.

Elderly
Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. A reduced initial dose of 1.25 mg ramipril should be considered.

Paediatric population
TRITACE is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

CONTRAINDICATIONS

- Hypersensitivity to the active substance, to any of the excipients or any other ACE (Angiotensin Converting Enzyme) inhibitors (see section 6.1)
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6)
- Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special populations
Pregnancy: ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

- *Patients at particular risk of hypotension*

- Patients with strongly activated renin-angiotensin-aldosterone system
Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:

- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

- *Transient or persistent heart failure post MI*

- *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*
The initial phase of treatment requires special medical supervision.

- *Elderly patients*

See section 4.2.

Surgery
It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function
Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).
In case of angioedema, TRITACE must be discontinued.
Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.
Intestinal angioedema has been reported in patients treated with ACE inhibitors including TRITACE (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

Anaphylactic reactions during desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of TRITACE should be considered prior to desensitization.

Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including TRITACE. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

Ethnic differences
ACE inhibitors cause higher rate of angioedema in black patients than in non black patients.
As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Contra-indicated combinations

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Precautions for use

Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim, tacrolimus, ciclosporin):
Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of TRITACE: Blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count: Increased likelihood of haematological reactions (see section 4.4).

Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

Non-steroidal anti-inflammatory drugs and acetylsalicylic acid: Reduction of the antihypertensive effect of TRITACE is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

PREGNANCY AND LACTATION

TRITACE is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Because insufficient information is available regarding the use of ramipril during breastfeeding (see section 5.2), ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).
This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

UNDESIRABLE EFFECTS

The safety profile of ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Adverse reactions frequency is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common	Uncommon	Rare	Very rare	Not known
Cardiac disorders		Myocardial ischaemia including angina pectoris or myocardial infarction,			

		tachycardia, arrhythmia, palpitations, oedema peripheral			
Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema,	Glossitis		Aphtous stomatitis

		abdominal pain upper including gastritis, constipation, dry mouth			
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased			
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis,	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Arthralgia			
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Vascular disorders	Hypotension, orthostatic blood pressure decreased, syncope	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon
General disorders and	Chest pain, fatigue	Pyrexia	Asthenia		

administration site conditions					
Immune system disorders					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
Hepatobiliary disorders		Hepatic enzymes and/or bilirubin conjugated increased,	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).
Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynaecomastia
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention

OVERDOSE

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: ACE Inhibitors, plain, ATC code C09AA05.

Mechanism of action

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and

tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.
Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Pharmacodynamic effects

Antihypertensive properties:
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.
In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.
The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.
Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Heart failure:
In addition to conventional therapy with diuretics and optional cardiac glycosides, ramipril has been shown to be effective in patients with functional classes II-IV of the New-York Heart Association. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

Clinical efficacy and safety

Cardiovascular prevention/Nephroprotection;

A preventive placebo-controlled study (the HOPE-study), was carried out in which ramipril was added to standard therapy in more than 9,200 patients. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level or cigarette smoking) were included in the study.
The study showed that ramipril statistically significantly decreases the incidence of myocardial infarction, death from cardiovascular causes and stroke, alone and combined (primary combined events).

The HOPE study: Main results

	Ramipril	Placebo	relative risk (95% confidence interval)	p-value
	%	%		
All patients	**n=4,645**	**N=4,652**		
Primary combined events	**14.0**	**17.8**	**0.78 (0.70-0.86)**	**<0.001**
Myocardial infarction	*9.9*	*12.3*	*0.80 (0.70-0.90)*	*<0.001*
Death from cardiovascular causes	*6.1*	*8.1*	*0.74 (0.64-0.87)*	*<0.001*
Stroke	*3.4*	*4.9*	*0.68 (0.56-0.84)*	*<0.001*

Secondary endpoints				
Death from any cause	*10.4*	*12.2*	*0.84 (0.75-0.95)*	*0.005*
Need for Revascularisation	*16.0*	*18.3*	*0.85 (0.77-0.94)*	*0.002*
Hospitalisation for unstable angina	*12.1*	*12.3*	*0.98 (0.87-1.10)*	*NS*
Hospitalisation for heart failure	*3.2*	*3.5*	*0.88 (0.70-1.10)*	*0.25*
Complications related to diabetes	*6.4*	*7.6*	*0.84 (0.72-0.98)*	*0.03*

The MICRO-HOPE study, a predefined substudy from HOPE, investigated the effect of the addition of ramipril 10 mg to the current medical regimen versus placebo in 3,577 patients at least ≥ 55 years old (with no upper limit of age), with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.
The primary analysis showed that 117 (6.5 %) participants on ramipril and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40], p = 0.027.
The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with ramipril on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g/24 h) or severe proteinuria (≥ 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in ramipril group) showed that the mean rate of GFR decline per month was lower with ramipril than with placebo; -0.54 (0.66) vs. -0.88 (1.03) ml/min/month, p = 0.038. The intergroup difference was thus 0.34 [0.03-0.65] per month, and around 4 ml/min/year; 23.1 % of the patients in the ramipril group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis or renal transplantation) vs. 45.5 % in the placebo group (p = 0.02).

Secondary prevention after acute myocardial infarction

The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The ramipril treatment was started 3 to 10 days after the acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in ramipril-treated patients was 16.9 % and in the placebo treated patients was 22.6 %. This means an absolute mortality reduction of 5.7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).

PHARMACOKINETIC PROPERTIES

Pharmacokinetics and Metabolism
Absorption

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %.
Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution
The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Metabolism
Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

Elimination
Excretion of the metabolites is primarily renal.
Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.
After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.
A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.

Patients with renal impairment (see section 4.2)
Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment (see section 4.2)
In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

PRECLINICAL SAFETY DATA

Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs.
Studies involving chronic oral administration have been conducted in rats, dogs and monkeys.
Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species.
As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d.
Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.
Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties.
Fertility was not impaired either in male or in female rats.
The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.
Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS

[To be completed nationally]

INCOMPATIBILITIES

[To be completed nationally]

SHELF LIFE

[To be completed nationally]

SPECIAL PRECAUTIONS FOR STORAGE

[To be completed nationally]

NATURE AND CONTENTS OF CONTAINER

[To be completed nationally]

SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]
{Name and address}
{tel}
{fax}
{e-mail}

MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TRITACE and associated names (see Annex I) 1.25 mg tablets
TRITACE and associated names (see Annex I) 2.5 mg tablets
TRITACE and associated names (see Annex I) 5 mg tablets
TRTACE and associated names (see Annex I) 10 mg tablets

TRITACE and associated names (see Annex I) 1.25 mg hard capsules
TRITACE and associated names (see Annex I) 2.5 mg hard capsules
TRITACE and associated names (see Annex I) 5 mg hard capsules
TRITACE and associated names (see Annex I) 10 mg hard capsules

[See Annex I - to be completed nationally]

ramipril

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
Hard Capsule

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{Tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

TRITACE and associated names (see Annex I) 1.25 mg tablets
TRITACE and associated names (see Annex I) 2.5 mg tablets
TRITACE and associated names (see Annex I) 5 mg tablets
TRITACE and associated names (see Annex I) 10 mg tablets

TRITACE and associated names (see Annex I) 1.25 mg capsules
TRITACE and associated names (see Annex I) 2.5 mg capsules
TRITACE and associated names (see Annex I) 5 mg capsules
TRITACE and associated names (see Annex I) 10 mg capsules

[See Annex I - To be completed nationally]

ramipril

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]
{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

TRITACE and associated names (see Annex I) 1.25 mg tablets
TRITACE and associated names (see Annex I) 2.5 mg tablets
TRITACE and associated names (see Annex I) 5 mg tablets
TRITACE and associated names (see Annex I) 10 mg tablets

TRITACE and associated names (see Annex I) 1.25 mg hard capsules
TRITACE and associated names (see Annex I) 2.5 mg hard capsules
TRITACE and associated names (see Annex I) 5 mg hard capsules
TRITACE and associated names (see Annex I) 10 mg hard capsules
[See Annex I – To be completed nationally]

Ramipril

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT TRITACE IS AND WHAT IT IS USED FOR

TRITACE contains a medicine called ramipril. This belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme Inhibitors).

TRITACE works by:
- Decreasing your body's production of substances that could raise your blood pressure
- Making your blood vessels relax and widen
- Making it easier for your heart to pump blood around your body.

TRITACE can be used:
- To treat high blood pressure (hypertension)
- To reduce the risk of you having a heart attack or stroke
- To reduce the risk or delay the worsening of kidney problems (whether or not you have diabetes)
- To treat your heart when it cannot pump enough blood to the rest of your body (heart failure)
- As treatment following heart attack (myocardial infarction) complicated with heart failure.

2. BEFORE YOU TAKE TRITACE

Do not take TRITACE:

- If you are allergic (hypersensitive) to ramipril, any other ACE inhibitor medicine or any of the ingredients of TRITACE listed in section 6.
  Signs of an allergic reaction may include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- If you have ever had a serious allergic reaction called "angioedema". The signs include itching, hives (urticaria), red marks on the hands, feet and throat, swelling of the throat and tongue, swelling around the eyes and lips, difficulty breathing and swallowing
- If you are having dialysis or any other type of blood filtration. Depending on the machine that is used, TRITACE may not be suitable for you
- If you have kidney problems where the blood supply to your kidney is reduced (renal artery stenosis)
- During the **last 6 months of pregnancy** (see section below on "Pregnancy and breast-feeding")
- If your blood pressure is abnormally low or unstable. Your doctor will need to make this assessment.

Do not take TRITACE if any of the above apply to you. If you are not sure, talk to your doctor before taking TRITACE.

Take special care with TRITACE

Check with your doctor or pharmacist before taking your medicine:

- If you have heart, liver or kidney problems
- If you have lost a lot of body salts or fluids (through being sick (vomiting), having diarrhoea, sweating more than usual, being on a low salt diet, taking diuretics (water tablets) for a long time or having had dialysis)
- If you are going to have treatment to reduce your allergy to bee or wasp stings (desensitization)
- If you are going to receive an anaesthetic. This may be given for an operation or any dental work. You may need to stop your TRITACE treatment one day beforehand; ask your doctor for advice
- If you have high amounts of potassium in your blood (shown in blood test results)
- If you have collagen vascular disease such as scleroderma or systemic lupus erythematosus
- You must tell your doctor if you think that you are (or might become) pregnant. TRITACE is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy, see section "Pregnancy and breast-feeding".

Children

TRITACE is not recommended for use in children and adolescents below 18 years of age because there is no information available in this population.

If any of the above apply to you (or you are not sure), talk to your doctor before taking TRITACE.

Taking TRITACE with other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription (including herbal medicines). This is because TRITACE can affect the way some other medicines work. Also some medicines can affect the way TRITACE works.

Please tell your doctor if you are taking any of the following medicines. They can make TRITACE work less well:

- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indometacin and aspirin)
- Medicines used for the treatment of low blood pressure, shock, cardiac failure, asthma or allergies such as ephedrine, noradrenaline or adrenaline. Your doctor will need to check your blood pressure.

Please tell your doctor if you are taking any of the following medicines. They can increase the chance of getting side effects if you take them with TRITACE:

- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indometacin and aspirin)
- Medicines for cancer (chemotherapy)
- Medicines to stop the rejection of organs after a transplant such as ciclosporin
- Diuretics (water tablets) such as furosemide
- Medicines which can increase the amount of potassium in your blood such as spironolactone, triamterene, amiloride, potassium salts and heparin (for thinning blood)
- Steroid medicines for inflammation such as prednisolone
- Allopurinol (used to lower the uric acid in your blood)
- Procainamide (for heart rhythm problems).

Please tell your doctor if you are taking any of the following medicines. They may be affected by TRITACE:
- Medicines for diabetes such as oral glucose lowering medicines and insulin. TRITACE may lower your blood sugar amounts. Check your blood sugar amounts closely while taking TRITACE
- Lithium (for mental health problems). TRITACE may increase the amount of lithium in your blood. Your lithium amount will need to be closely checked by your doctor.

If any of the above apply to you (or you are not sure), talk to your doctor before taking TRITACE.

Taking TRITACE with food and alcohol
- Drinking alcohol with TRITACE may make you feel dizzy or light-headed. If you are concerned about how much you can drink while you are taking TRITACE, discuss this with your doctor as medicines used to reduce blood pressure and alcohol can have additive effects.
- TRITACE may be taken with or without food.

Pregnancy and breast-feeding
You must tell your doctor if you think that you are (or might become) pregnant
You should not take TRITACE in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby.
If you become pregnant while on TRITACE, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.
You should not take TRITACE if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You may feel dizzy, while taking TRITACE. This is more likely to happen when you start taking TRITACE or start taking a higher dose. If this happens, do not drive or use any tools or machines.

3. HOW TO TAKE TRITACE

Always take TRITACE exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Take this medicine by mouth at the same time of the day each day.
- Swallow the tablets/capsules whole with liquid.
- Do not crush or chew the tablets/capsules.

How much to take

Treatment of high blood pressure
- The usual starting dose is 1.25 mg or 2.5 mg once daily.

- Your doctor will adjust the amount you take until your blood pressure is controlled.
- The maximum dose is 10 mg once daily.
- If you are already taking diuretics (water tablets), your doctor may stop or reduce the amount of the diuretic you take before beginning treatment with TRITACE.

To reduce the risk of you having a heart attack or stroke
- The usual starting dose is 2.5 mg once daily.
- Your doctor may then decide to increase the amount you take.
- The usual dose is 10 mg once daily.

Treatment to reduce or delay the worsening of kidney problems
- You may be started on a dose of 1.25 mg or 2.5 mg once daily.
- Your doctor will adjust the amount you are taking.
- The usual dose is 5 mg or 10 mg once daily.

Treatment of heart failure
- The usual starting dose is 1.25 mg once daily.
- Your doctor will adjust the amount you take.
- The maximum dose is 10 mg daily. Two administrations per day are preferable.

Treatment after you have had a heart attack
- The usual starting dose is 1.25 mg once daily to 2.5 mg twice daily.
- Your doctor will adjust the amount you take.
- The usual dose is 10 mg daily. Two administrations per day are preferable.

Elderly
Your doctor will reduce the initial dose and adjust your treatment more slowly.

If you take more TRITACE than you should
Tell a doctor or go to the nearest hospital casualty department straight away. Do not drive to the hospital, get somebody else to take you or call for an ambulance. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take TRITACE
- If you miss a dose, take your normal dose when it is next due.
- Do not take a double dose to make up for a forgotten tablet/capsule.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, TRITACE can cause side effects, although not everybody gets them.
Stop taking TRITACE and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:
- Swelling of the face, lips or throat which make it difficult to swallow or breathe, as well as itching and rashes. This could be a sign of a severe allergic reaction to TRITACE
- Severe skin reactions including rash, ulcers in your mouth, worsening of a pre-existing skin disease, reddening, blistering or detachment of skin (such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiform).

Tell your doctor immediately if you experience:
- Faster heart rate, uneven or forceful heartbeat (palpitations), chest pain, tightness in your chest or more serious problems including heart attack and stroke
- Shortness of breath or a cough. These could be signs of lung problems
- Bruising more easily, bleeding for longer than normal, any sign of bleeding (e.g. bleeding from the gums), purple spots blotching on the skin or getting infections more easily than usual, sore throat and

fever, feeling tired, faint, dizzy or having pale skin. These can be signs of blood or bone marrow problems
- Severe stomach pain which may reach through to your back. This could be a sign of pancreatitis (inflammation of the pancreas).
- Fever, chills, tiredness, loss of appetite, stomach pain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage.

Other side effects include:
Please tell your doctor if any of the following gets serious or lasts longer than a few days.

Common (affects less than 1 in 10 people)
- Headache or feeling tired
- Feeling dizzy. This is more likely to happen when you start taking TRITACE or start taking a higher dose
- Fainting, hypotension (abnormally low blood pressure), especially when you stand or sit up quickly
- Dry tickly cough, inflammation of your sinuses (sinusitis) or bronchitis, shortness of breath
- Stomach or gut pain, diarrhoea, indigestion, feeling or being sick
- Skin rash with or without raised area
- Chest pain
- Cramps or pain in your muscles
- Blood tests showing more potassium than usual in your blood.

Uncommon (affects less than 1 in 100 people)
- Balance problems (vertigo)
- Itching and unusual skin sensations such as numbness, tingling, pricking, burning or creeping on your skin (paraesthesia)
- Loss or change in the way things taste
- Sleep problems
- Feeling depressed, anxious, more nervous than usual or restless
- Blocked nose, difficulty breathing or worsening of asthma
- A swelling in your gut called “intestinal angioedema” presenting with symptoms like abdominal pain, vomiting and diarrhoea
- Heartburn, constipation or dry mouth
- Passing more water (urine) than usual over the day
- Sweating more than usual
- Loss or decrease of appetite (anorexia)
- Increased or irregular heartbeatsSwollen arms and legs. This may be a sign of your body holding onto more water than usual
- Flushing
- Blurred vision
- Pain in your joints
- Fever
- Sexual inability in men, reduced sexual desire in men or women
- An increased number of certain white blood cells (eosinophilia) found during a blood test
- Blood tests showing changes in the way your liver, pancreas or kidneys are working.

Rare (affects less than 1 in 1,000 people)
- Feeling shaky or confused
- Red and swollen tongue
- Severe flaking or peeling of the skin, itchy, lumpy rash
- Nail problem (e.g. loosening or separation of a nail from its bed)

- Skin rash or bruising
- Blotches on your skin and cold extremities
- Red, itchy, swollen or watery eyes
- Disturbed hearing and ringing in your ears
- Feeling weak
- Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets or in the amount of haemoglobin.

Very rare (affects less than 1 in 10,000 people**)**
- Being more sensitive to the sun than usual.

Other side effects reported:
Please tell your doctor if any of the following gets serious or lasts longer than a few days.
- Difficulty concentrating
- Swollen mouth
- Blood tests showing too few blood cells in your blood
- Blood tests showing less sodium than usual in your blood
- Fingers and toes changing colour when you are cold and then tingling or feeling painful when you warm up (Raynaud's phenomenon)
- Breast enlargement in men
- Slowed or impaired reactions
- Burning sensation
- Change in the way things smell
- Hair loss.

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TRITACE

[To be completed nationally]

6. FURTHER INFORMATION

What TRITACE.contains
[To be completed nationally]

What TRITACE looks like and contents of the pack
Tablets, hard capsules
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:
Tritace 1.25 mg Tabletten, Tritace 2.5 mg Tabletten, Tritace 5 mg Tabletten, Tritace 10 mg Tabletten
Hypren 1.25 mg Kapseln, Hypren 2.5 mg Kapseln, Hypren 5 mg Kapseln,
Hypren 10 mg Tabletten

Belgium:
Tritace 1.25 mg tabletten/comprimés/ Tabletten, Tritace 2.5 mg tabletten/comprimés/ Tabletten , Tritace 5 mg tabletten/comprimés/ Tabletten , Tritace 10 mg tabletten/comprimés/ Tabletten ,
Tritace 10 mg capsules/gellules/Kapseln
Ramace 1.25 mg tabletten/comprimés/ Tabletten , Ramace 2.5 mg tabletten/comprimés/ Tabletten , Ramace 5 mg tabletten/comprimés/ Tabletten

Bulgaria:
Tritace 2.5 mg таблетки, Tritace 5 mg таблетки, Tritace 10 mg таблетки

Cyprus:
Triatec 2.5 mg δισκία, Triatec 5 mg δισκία, Triatec 10 mg δισκία

Czech Republic:
Tritace 1.25 mg tablety, Tritace 2.5 mg tablety, Tritace 5 mg tablety, Tritace 10 mg tablety
Ramipril Winthrop 1.25 mg tobolky, Ramipril Winthrop 2.5 mg tobolky, Ramipril Winthrop 5 mg tobolky,

Denmark:
Triatec 1.25 mg tabletter, Triatec 2.5 mg tabletter, Triatec 5 mg tabletter,
Triatec 10 mg kapsler

Estonia :
Cardace 2.5 mg tabletid, Cardace 5 mg tabletid, Cardace 10 mg tabletid

Finland:
Cardace 1.25 mg tabletit, Cardace 2.5 mg tabletit, Cardace 5 mg tabletit, Cardace 10 mg tabletit,
Cardace 10 mg kapselit
Ramipril Medgenerics 1.25 mg tabletit, Ramipril Medgenerics 2.5 mg tabletit, Ramipril Medgenerics 5 mg tabletit, Ramipril Medgenerics 10 mg tabletit

France:
Triatec 1.25 mg comprimés, Triatec 2.5 mg comprimés, Triatec 5 mg comprimés, Triatec 10 mg comprimés
Triateckit 2.5 mg comprimés, Triateckit 5 mg comprimés, Triateckit 10 mg comprimés
Ramikit 2.5 mg comprimés, Ramikit 5 mg comprimés, Ramikit 10 mg comprimés
Triatec faible 1.25 mg gélules
Triatec 2.5 mg gélules, Triatec 5 mg gélules
Ramipril Winthrop 1.25 mg comprimés, Ramipril Winthrop 2.5 mg comprimés, Ramipril Winthrop 5 mg comprimés, Ramipril Winthrop 10 mg comprimés

Germany:
Delix 2.5 mg Tabletten, Delix 5 mg Tabletten, Delix 10 mg Tabletten
Delix Protect Startset
Ramilich 2.5 mg Tabletten, Ramilich 5 mg Tabletten, Ramilich 10 mg Tabletten
Ramilich Startset
Delix 1.25 mg Tabletten,
Delix 1.25 mg Kapseln, Delix 2.5 mg Kapseln, Delix 5 mg Kapseln, Delix 10 mg Kapseln
Vesdil 1.25 mg Kapseln, Vesdil 2.5 mg Kapseln, Vesdil 5 mg Kapseln,
Vesdil 1.25 mg Tabletten, Vesdil 2.5 mg Tabletten

Vesdil N 2.5 mg Tabletten, Vesdil N 5 mg Tabletten
Vedil 5 mg Tabletten
Vesdil Protect 10 mg Tabletten

Greece:
Triatec 1.25 mg δισκία, Triatec 2.5 mg δισκία, Triatec 5 mg δισκία

Hungary:
Tritace Mite 1.25 mg tabletta
Tritace 2.5 mg tabletta, Tritace 5 mg tabletta, Tritace 10 mg tabletta
Ramipril Prevent 1.25 mg tabletta, Ramipril Prevent 2.5 mg tabletta, Ramipril Prevent 5 mg tabletta, Ramipril Prevent 10 mg tabletta
Ramiwin 1.25 mg tabletta, Ramiwin 2.5 mg tabletta, Ramiwin 5 mg tabletta, Ramiwin 10 mg tabletta

Ireland:
Tritace 1.25 mg tablets, Tritace 2.5 mg tablets, Tritace 5 mg tablets, Tritace 10 mg tablets,
Tritace 1.25 mg capsules, Tritace 2.5 mg capsules, Tritace 5 mg capsules, Tritace 10 mg capsules
Loavel 1.25 mg tablets, Loavel 2.5 mg tablets, Loavel 5 mg tablets, Loavel 10 mg tablets,
Loavel 1.25 mg capsules, Loavel 2.5 mg capsules, Loavel 5 mg capsules, Loavel 10 mg capsules
Ramipril 1.25 mg tablets, Ramipril 2.5 mg tablets, Ramipril 5 mg tablets, Ramipril 10 mg tablets,
Ramipril 1.25 mg capsules, Ramipril 2.5 mg capsules, Ramipril 5 mg capsules, Ramipril 10 mg capsules

Italy:
Triatec 1.25 mg compresse, Triatec 2.5 mg compresse, Triatec 5 mg compresse, Triatec 10 mg compresse
Ramipril sanofi-aventis 2.5 mg compresse, Ramipril sanofi-aventis 5 mg compresse, Ramipril sanofi-aventis 10 mg compresse
Unipril 1.25 mg compresse, Unipril 2.5 mg compresse, Unipril 5 mg compresse, Unipril 10 mg compresse
Quark 1.25 mg compresse, Quark 2.5 mg compresse, Quark 5 mg compresse, Quark 10 mg compresse

Latvia:
Cardace 2.5 mg tabletes, Cardace 5 mg tabletes, Cardace 10 mg tabletes

Lithuania:
Cardace 2.5 mg tabletės, Cardace 5 mg tabletės, Cardace 10 mg tabletės

Luxembourg:
Tritace 1.25 mg tabletten/comprimés/ Tabletten, Tritace 2.5 mg tabletten/comprimés/ Tabletten , Tritace 5 mg tabletten/comprimés/ Tabletten, Tritace 10 mg tabletten/comprimés/ Tabletten ,
Tritace 10 mg capsules/gellules/Kapseln
Ramace 1.25 mg tabletten/comprimés/ Tabletten , Ramace 2.5 mg tabletten/comprimés/ Tabletten , Ramace 5 mg tabletten/comprimés/ Tabletten

Netherlands:
Tritace 1.25 mg tabletten, Tritace 2.5 mg tabletten, Tritace 5 mg tabletten, Tritace 10 mg tabletten,
Tritace 1.25 mg capsules, Tritace 2.5 mg capsules, Tritace 5 mg capsules, Tritace 10 mg capsules

Norway:
Triatec 1.25 mg tabletter, Triatec 2.5 mg tabletter, Triatec 5 mg tabletter, Triatec 10 mg tabletter,
Triatec 10 mg capsules,
Ramipril Winthrop 1.25 mg tabletter, Ramipril Winthrop 2.5 mg tabletter, Ramipril Winthrop 5 mg tabletter, Ramipril Winthrop 10 mg tabletter

Poland:

Tritace 2.5 mg tabletki, Tritace 5 mg tabletki, Tritace 10 mg tabletki

Portugal:
Triatec 1.25 mg comprimidos, Triatec 2.5 mg comprimidos, Triatec 5 mg comprimidos, Triatec 10 mg comprimidos,
Triatec 1.25 mg cápsulas, Triatec 2.5 mg cápsulas, Triatec 5 mg cápsulas, Triatec 10 mg cápsulas

Romania:
Tritace 2.5 mg comprimate, Tritace 5 mg comprimate, Tritace 10 mg comprimate
Zenra 2.5 mg comprimate, Zenra 5 mg comprimate, Zenra 10 mg comprimate

Slovak Republic:
Tritace 1.25 mg tablety, Tritace 2.5 mg tablety, Tritace 5 mg tablety, Tritace 10 mg tablety

Slovenia:
Tritace 1.25 mg tablete, Tritace 2.5 mg tablete, Tritace 5 mg tablete, Tritace 10 mg tablete

Spain:
Acovil 1.25 mg comprimidos, Acovil 2.5 mg comprimidos, Acovil 5 mg comprimidos, Acovil 10 mg comprimidos

Sweden:
Triatec 1.25 mg tabletter, Triatec 2.5 mg tabletter, Triatec 5 mg tabletter, Triatec 10 mg tabletter,
Triatec Hope tabletter
Triatec start tabletter
Ramipril Winthrop 1.25 mg tabletter, Ramipril Winthrop 2.5 mg tabletter, Ramipril Winthrop 5 mg tabletter, Ramipril Winthrop 10 mg tabletter
Pramace 1.25 mg tabletter, Pramace 2.5 mg tabletter, Pramace 5 mg tabletter, Pramace 10 mg tabletter, Pramace 10 mg kapslar

United Kingdom
Tritace 1.25 mg tablets, Tritace 2.5 mg tablets, Tritace 5 mg tablets, Tritace 10 mg tablets,
Tritace 1.25 mg capsules, Tritace 2.5 mg capsules, Tritace 5 mg capsules, Tritace 10 mg capsules
Tritace Titration Pack capsules,
Tritace Titration Pack tablets

This leaflet was last approved in {MM/YYYY}
[To be completed nationally]

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.